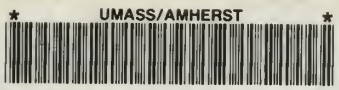

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Center for Health Promotion and
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TO: Elaine Krueger, M.P.H., Acting Director
Division of Environmental Epidemiology and Toxicology

FROM: Martha Steele, M.P.H.

RE: Permethrin Health Effects

DATE: November 7, 1985

This memo is a brief review of health information on permethrin.

METABOLISM

Permethrin is rapidly metabolized to more polar materials which are excreted. Only small amounts of the chemical are taken up by adipose tissue. They are eliminated when exposure ceases (FAO/WHO, 1981).

ACUTE EFFECTS

The rat oral LD50 for permethrin ranges from 1000 to 8500 mg/kg (EPA, 1982). This indicates a moderate or slightly toxic compound. In developing a non-carcinogenic No-Observed-Effect-Level (NOEL) for rats (5 mg/kg/day) and mice (50 mg/kg/day), the effects seen at higher levels were increases in liver and kidney weights, and pathological changes in the liver (EPA, 1982; FAO/WHO, 1981).

The most common acute symptoms seen in worker populations exposed to permethrin include skin and respiratory tract irritation (Kolmodin et al., 1982; Flanagan and Tucker, 1983; Le Quesne et al., 1981).

CHRONIC

Carcinogenicity

A review of oncogenicity studies conducted between 1977 and 1980 on permethrin was carried out by the EPA's Office of Pesticide Programs (OPP) in 1982 when they were considering food tolerances for permethrin. OPP

asked its Scientific Advisory Panel (SAP) to also review the studies. All studies were dietary, unpublished, and sponsored by the manufacturers of permethrin. The studies, as presented by OPP, are summarized below.

Mice - Three studies in three different Swiss-derived strains of mice were conducted.

1. Alderly Park strain (ICI study) - No significant tumor increases were seen at dose levels of 0, 37.5, 150, and 300 mg/kg. A significant dose-response trend in benign lung tumors, or adenomas, in males was seen, but no significant differences between controls and any of the dose groups in either sex were seen. Furthermore, the incidence of lung tumors was well within historical control levels seen in Swiss-derived mice (EPA OPP, 1982).

2. CFLP mice (BW study) - Levels in this study were 0, 10, 50, and 250 mg/kg. A significant dose-response trend in females in lung adenomas was seen, due largely to an increase in the high-dose group. A significant difference in the incidence of lung adenomas was seen between controls and the high dose group only (3/96 vs. 15/74).

3. CD-1 mice (FMC II study) - The dose levels for females were 0, 3, 375, and 750 mg/kg. A significant dose-response trend in females in lung neoplasms (adenomas/carcinomas (malignant tumors) combined: 15/74, 24/72, 35/74, 44/75) was seen. The trend applied to both carcinomas and carcinomas/adenomas combined. For adenomas and carcinomas combined, a significant difference between controls and each of the two highest dose groups was seen. For carcinomas only, it was significant in the high dose group only. There was also a significant dose-response trend in females in the incidence of benign liver tumors (hepatomas), but no significant difference between the treatment groups in malignant tumors (hepatocellular carcinomas). In hepatomas, there was a significant difference between the controls and the two highest dose groups (6/74 vs. 25/76 and 30/75).

The SAP concluded that the data in this study was uninterpretable, due to problems of intercurrent disease, no clear indication of tissue examinations by the pathologist during gross examination, and the selection of tissue for histology. The OPP mentioned none of these problems in its report, although they did say that the EPA and FDA conducted a joint audit of this study and concluded that no problem was serious enough to compromise the usefulness of the study for oncogenic evaluation (EPA OPP, pg. 12, 1982).

Rats - Two studies have been carried out in Wistar rats with non-positive results at dose levels as high as 375 mg/kg/day. One other study was carried out in the Long-Evans strain at dose levels up to 500 mg/kg. EPA concluded

there was suggestive evidence of an increase in lung tumors in male rats, but due to serious flaws in the histological evaluations, the study could not be well evaluated. The SAP did not feel this study could be used at all.

Mutagenicity

A battery of mutagenicity tests (including about 9 different tests) have all been negative. The endpoints tested included gene mutation, chromosomal aberration, and DNA damage and repair. Thus, permethrin has not been shown to be mutagenic (EPA, 1982; FAO/WHO, 1981).

Teratogenicity/Reproductive Effects

Permethrin has not been shown to be teratogenic nor to produce reproductive effects (EPA, 1982; FAO/WHO, 1981). Four teratology studies in rats, mice,or rabbits at levels ranging up to 400 mg/kg/day have been conducted, and three 3-generation reproduction studies at dosages up to 180 mg/kg/day have all been non-positive where maternal effects were not seen (EPA, 1982).

Summary on Carcinogenicity Evidence

The carcinogenicity evidence on permethrin is both strengthened and weakened by a number of factors. These are outlined below:

Evidence Strengthened

1. At least suggestive evidence of lung tumors in two different strains of mice exists.
2. Lung tumors showed a significant dose-response trend in the mouse studies, suggesting a treatment-related effect.
3. A positive result at a second site, the liver, was seen in one study in female mice only. Hepatomas seen in this study were of a higher incidence than seen in historical controls in this strain. While there is controversy about "benign-only" findings, there is a large segment of the scientific community that believes truly benign tumors in rodents are rare and that tumors diagnosed as benign are really part of the progression to malignancy (OSTP, 1985).

Evidence Weakened

1. Clear positive results occurred in only one sex of one species.
2. A significant difference between controls and dose groups occurred only at the highest dose levels.
3. According to the OPP, no decrease in latency period was seen in any study.
4. In the CD-1 mouse strain, historical control data show that the incidence of lung adenomas in females reviewed here fell within the range of the incidence in historical controls.
5. A battery of mutagenicity tests have all been non-positive for permethrin.
6. No positive teratogenicity or reproductive tests have been reported.

Pertaining to the carcinogenicity of permethrin, the EPA concluded: "The biological evidence produced by long-term mouse and rat studies, and other toxicological studies leads the EPA to conclude, based on the Agency risk assessment, that the likelihood of oncogenic effects in humans from exposure to low levels of permethrin is non-existent or extremely low. Thus, even if permethrin is a human oncogen (which is unlikely), it is highly unlikely that it would present a significant risk to humans at the levels to which they will be exposed" (EPA, 1982, pg. 45009).

The SAP concluded, "The Panel thus expressed the view that, based on all the data together, the oncogenic potential of permethrin was very weak. The possibility of oncogenic potential in man was extremely remote" (SAP, 1981).

ROUTE OF EXPOSURE

In termite applications, the two main routes of exposure are usually skin absorptionand inhalation. Permethrin does not appear to be easily absorbed through the skin. In one study, a powder containing permethrin was used to control body lice in village populations in Egypt. The powder was applied to the skin as well as to selected pieces of furniture in the home. The authors concluded the maximal amount absorbed by all routes was only about 1% of the applied dose (Nassif et al., 1980). In another study conducted by the Environmental Hygiene Agency of the U.S. Army, the authors concluded that skin absorption of permethrin in man should be less than 8% of the applied dose (U.S. Army, 1982). The conclusion was based on studies in both rats and dogs.

We know of no data on air levels that might be found after termite control applications. Permethrin has a vapor pressure of 3.4×10^{-7} mm Hg at 25 C (Agrochemicals Handbook, 1983). This compares to chlordane's vapor pressure of 1×10^{-5} mm Hg at 20 C. Ethanol, a volatile substance, has a vapor pressure of 43.9 mm Hg at 20 C (Verschueren, 1983). Thus, permethrin is not very volatile.

It therefore appears that, with correct application, little exposure to permethrin would occur.

OTHER STATES

New York State has registered permethrin as a termiticide, according to the DEC's Frank Hegener. The state has not, however, carried out any health review on permethrin. The registration was granted based on the fact that the EPA granted a registration for this use.

CONCLUSIONS

Permethrin has shown positive results in female mice in lung tumors and hepatomas in one study, and in another study, female mice had a signifcant elevation in the high dose group only (250 mg/kg) of lung adenomas. No positive results have been shown in other species. No positive results have occurred in mutagenicity and teratogenicity tests.

Permethrin has a low acute toxicity. It is rapidly metabolized in the body, and not easily abosrbed through the skin. In a termite control application, the major route of exposure is expected to be inhalation. Permethrin is not, however, very volatile. Thus, minimal exposure is expected to occur with correct application.

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